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MEMORANDUM

SUBJECT: ***CADUSAFOS*** **-** Report of the FQPA Safety Factor Committee.

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THROUGH: Ed Zager, Chairman
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The Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) convened on May 12-14, 1998 and conducted a comprehensive review of 40 organophosphates. The FQPA Safety Factor Committee on June 15 and 16, 1998 evaluated the hazard and exposure data and recommend application of the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides. The Committee recommended that for cadusafos, the 10-fold safety factor for protection of infants and children should be reduced (to 3x).

I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) convened on May 12-14, 1998 to conduct a comprehensive review of 40 organophosphates which were originally reviewed by this committee over the period of September 1997 through May 1998.

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and exposure data for and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

This report presents a summary of the hazard and exposure assessment, as well as the FQPA safety factor recommendation for cadusafos.

II. HAZARD ASSESSMENT

Hazard assessment for determining the increased susceptibility for infants and children from exposure to cadusafos considered: 1) adequacy of the toxicology database; 2) evaluation of organophosphate induced delayed neurotoxicity (OPIDN) in hens; 3) evidence of neurotoxicity following single and multiple oral dosing; 4) indication of increased susceptibility following *in utero* exposure in the prenatal developmental toxicity studies in rats and rabbits and/or post natal exposure in the two generation reproduction study in rats; and 5) the need for a developmental neurotoxicity study in rats.

A. Adequacy of Toxicology Database

The toxicology database is inadequate according to the Subdivision F Guideline requirements for a food-use chemical. Data gaps exists for acute and subchronic neurotoxicity studies in rats. The HIARC placed the requirement for a developmental neurotoxicity study **in reserve** for cadusafos.

B. Evaluation of Neurotoxicity

In an acute delayed neurotoxicity study, hens received an oral administration of a single dose of cadusafos at 8 mg/kg/day. Cadusafos did not cause delayed neurotoxicity. The HIARC members noted that the neuropathology data was not available for review. However, the neuropathology data was made available after the meeting and showed no evidence of neuropathology in hens exposed to cadusafos. It is noted that this study did not assess for the potential of cadusafos to inhibit neurotoxic esterase (NTE) in hens. (MRID No. 00255691).

No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, FOB, and histopathology on the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to cadusafos.

C. Developmental Toxicity

In a developmental toxicity study pregnant Sprague-Dawley rats received oral doses of cadusafos at 0, 2, 6 or 18 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 6 mg/kg/day and the LOEL was 18 mg/kg/day based on cholinergic signs including diarrhea, decreased locomotion, tremors, lacrimation, exothalmus and fasciculation. For developmental toxicity, the NOEL was 6 mg/kg/day and the LOEL was 18 mg/kg/day based on decreased fetal body weight. There was no evidence of teratogenicity (MRID No. 00159057).

In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of cadusafos 0, 0.1, 0.3, or 0.9 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 0.3 mg/kg/day and the LOEL was 0.9 mg/kg/day based on mortality and clinical signs of toxicity including ataxia, dyspnea and prostration. For developmental toxicity, the NOEL was 0.3 mg/kg/day and the LOEL 0.9 mg/kg/day based on an increase in the total number of resorptions, a decrease in the total number of fetuses compared to controls and fetal death. There was no evidence of teratogenicity (MRID No. 00159058).

D. Reproductive Toxicity

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing cadusafos at 0, 0.1, 0.5 or 5 ppm (0, 0.005, 0.025, or 0.25 mg/kg/day) for two successive generations. For parental systemic toxicity, the NOEL was 0.5 ppm (0.025 mg/kg/day) and the LOEL was 5 ppm (0.25 mg/kg/ day) based on significant inhibition of plasma and red blood cell cholinesterase activity. For reproductive toxicity, the NOEL was 0.005 mg/kg/day and the LOEL was 0.025 mg/kg/day based on a statistically significant decrease in live birth index (MRID 41441803).

The lower NOEL (0.005 mg/kg/day) for offspring toxicity when compared to the parental systemic toxicity NOEL (0.025 mg/kg/day) indicated an apparent increase in susceptibility to the offspring following exposure to cadusafos. Although there were statistically significant decrease in live birth index in the mid and high dose groups of the F2B generation, the biologically relevance of the effects are unclear because:1) the decreased in live birth index for the mid (96% live birth) and high dose (95% live birth) groups was reflective of the unusually high observed F_{2B} control group (99% live birth); 2) the live birth index for the F_{2B} mid and high dose group were well within the range of the F_{2A} control group (92% live birth) or F_{1A} (95%) or F_{1B} (93%) control groups; and 3) the decrease in live birth index was not consistent across the F_{2A} and F_{2B} generations.

Although there is an apparent dose-related decrease in live birth index in the F_{2B} generation, there was no such incident pattern observed in any other generation (e.g. F_{1A} and F_{1B} or F_{2A} and F_{2B}). Based on these facts, the reproductive toxicity and developmental toxicity NOEL was 0.25 mg/kg/day, the highest dose tested. There was no increased sensitivity to pups over the adults.

E. Determination of Developmental Neurotoxicity Study

The HIARC placed the requirement for a developmental neurotoxicity study **in reserve**. Data available to assess the potential developmental neurotoxicity of cadusafos are limited due to the lack of neurotoxicity (acute and subchronic) studies in rats. Data from these studies are used for hazard characterization as well as in determining the need for a developmental neurotoxicity study. The "trigger" for a developmental neurotoxicity study for example, will be "positive" histopathology in these studies as well as central nervous system effects (e.g., decrease in brain weights) in these or other toxicology studies (e.g., 90-day or chronic studies). When a developmental neurotoxicity study is required, it is because this study will provide additional data (e.g., functional parameter development, potential increased susceptibility, effects on the development of the fetal nervous system, etc.). When the requirement for a developmental neurotoxicity study is placed in reserve status, the Agency will make the final requirement decision following evaluation of the results of the neurotoxicity studies.

F. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility or rat or rabbit fetuses to *in utero* exposure to cadusafos. There was no indication of increased susceptibility in the offspring as compared to parental animals in the two generation reproduction study. In these studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

G. Data Gaps

Acute Neurotoxicity Study in Rats (§81-8)
Subchronic Neurotoxicity Studies in Rats (§82-7)
Developmental Neurotoxicity Study in Rats (§83-6) - In reserve.

III. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

The exposure assessment addresses the potential for exposure to infants and children from pesticide residues in food, drinking water, and residential uses. Considerations include: 1) the evaluation of use patterns; 2) actual exposure data or estimates; and 3) the completeness of the data, including characterization of uncertainties pertaining to exposure from these sources.

A. Dietary Exposure Considerations

Cadusafos is used for broad spectrum control of plant parasitic nematodes and soil insects by contact action. A permanent tolerance has been established for residues of cadusafos, *per se*, in/on bananas at 0.01 ppm imported to the United States (40 CFR §180.461). There are no U.S. registrations as of May 10, 1994 for the nematicide/insecticide, cadusafos.

The Codex Alimentarius Commission has proposed maximum residue limits (MRLs) for residues of cadusafos, *per se*, in/on bananas at 0.01 ppm and potatoes at 0.02 ppm. The

U.S. and Codex are in harmony with respect to tolerance expression. The reassessed U.S. tolerance on bananas at 0.01 ppm is in harmony with the proposed Codex MRLs on bananas.

For chronic dietary analysis, the dietary exposure analysis system uses ½ LOD rather than the tolerance level. FDA monitoring data suggest residues of cadusafos are not likely to be greater than 0.001 ppm (LOD) in/on imported bananas since the multi residue methods (MRMs) capable of detecting cadusafos in/on bananas have not found the pesticide after screening hundreds of samples from approximately a dozen countries since 1993. Considering the fact that most bananas are eaten or processed with the peel removed and that available data showed no detectable residues in the pulp after exaggerated applications, a value of ½ LOD (0.0005 ppm) is appropriate for the dietary exposure estimate. Percent of crop treated data (%CT) for bananas were also used in calculation of the chronic dietary exposure analysis for cadusafos. Refining the analysis using %CT data along with ½ LOD residue levels result in more realistic estimates of chronic dietary exposure to cadusafos in imported bananas.

For acute dietary analysis, the dietary exposure analysis system uses only tolerance level residues for bananas which results in a probable overestimate of acute dietary exposure.

B. Drinking Water Exposure Considerations

A drinking water exposure assessment was not performed for cadusafos since there are no domestic uses for this pesticide and therefore, no potential exists for ground and/or surface water contamination.

C. Residential Exposure Considerations

Cadusafos is not currently registered for residential use.

IV. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

Initially, the HIARC and the FQPA Safety Factor Committee in their respective meetings, determined that the 10x safety factor should be retained for cadusafos because of datagaps for neurotoxicity studies in the hens and rats, as well as for the placement of the developmental neurotoxicity study in rats **in reserve**.

However, following these meetings, data for the acute delayed neurotoxicity was made available which made this study acceptable and satisfactory for the Guideline requirement §81-7. Taking this information in consideration, on September 22, 1998, the FQPA Safety Factor Committee recommended that the **10x factor** for protection of infants and children (as required by FQPA) should be **reduced to 3x** for cadusafos.

B. Rationale for Reduction of the FQPA Safety Factor

In general, hazard (based on the neurotoxicity, developmental, and reproductive toxicity studies) and exposure (dietary, drinking water, and residential) assessments indicate:

1. In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

2. In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

3. There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies submitted to the Agency.

4. Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary exposure (no drinking water or residential assessment is required for cadusafos).

The Committee determined that the FQPA safety factor is required, however, the 10x could be reduced to 3x based on the data gaps for acute and subchronic neurotoxicity studies in rats. Subsequently, the requirement of a developmental neurotoxicity study is placed in **reserve** status.

C. Identification of Population Subgroup

The Committee determined that the FQPA Safety Factor (3x) factor is applicable for the following the subpopulations:

1. **Acute Dietary:** All populations which include Infants and Children.

2. **Chronic Dietary:** All populations which include Infants and Children.

3. **Residential Exposure:** There are currently no registered residential uses.

The FQPA safety factors are relevant for acute and chronic dietary risk assessments since the toxicology endpoints are based on plasma, red blood cell, and/or brain cholinesterase inhibition seen following single (acute) and/or repeated (chronic) exposures. Also, the lack of a complete data base encompasses the general population and is not limited to any one subpopulation.

V. SUMMARY OF TOXICOLOGY ENDPOINTS SELECTION

The doses and toxicological endpoints selected for dietary exposure scenarios are summarized below. For details on the endpoint selection refer to the HIARC reports for cadusafos (HED Doc. No. 012345 and 012621).

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL=0.02	Inhibition of plasma cholinesterase activity in both sexes of dogs seen by Day3	14-day Toxicity-Dog
Chronic Dietary	NOEL=0.001	Inhibition of plasma cholinesterase activity in both sexes of dogs.	Chronic Toxicity-Dog
Residential	Import tolerance; residential exposure risk assessments are not required.		